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CARBODIIMIDES

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Perhaps one of the most versatile synthetic tools at the disposal of the organic chemist is the aliphatic and aromatic carbodiimide ($RN=C=NR'$; R,R' = alkyl or aryl). Substituted carbodiimides have been applied successfully to the synthesis of amides (1), esters (2), pyrophosphates (3), sulfonic (4) and carboxylic (5) anhydrides, N-alkyl- and N-arylisomaleimides (6), amidines (7), and a variety of other compounds. Certain aromatic carbodiimides are useful reagents for the characterization of carboxylic acids (8).

Here, also, is a chemical reagent of considerable value to the biochemist, for carbodiimides have been utilized in the formation of peptide linkages (1, 9), in the synthesis of nucleoside polyphosphates (10), in the synthesis of a phosphorylating reagent (11), and in the selective degradation of certain peptides (12).

For a comprehensive review of the chemistry of carbodiimides prior to 1953, *The Chemistry of Carbodiimides*, by H. G. Khorana is recommended to the reader (13).

Structure

Although carbodiimide ($HN=C=NH$) probably exists mainly in the tautomeric form cyanamid (H_2NCN) (14), the disubstituted carbodiimides are structurally related to the unsaturated allenes ($=C=C=C=$), isocyanates ($-N=C=O$), ketenes ($=C=C=O$), and ketenimines ($=C=C=N-$). The infrared spectra of dicyclohexyl-, di-*p*-tolyl-, and di-*p*-dimethylaminophenylcarbodiimide (13) show a strong absorption band at 4.75 to 4.77 μ which appears to be characteristic of $-N=C=N-$ stretching. The characteristic absorption band for the allenes is at 5 to 5.16 μ (15) and for the ketenimines at 5 μ (16).

Methods of Preparation

Carbodiimides have been prepared by several different methods, but desulfurization of disubstituted thioureas is the method most widely used. Symmetrical thioureas may be prepared by reaction of amines with carbon disulfide (17), while unsymmetrical thioureas may be prepared by treatment of isothiocyanates with amines (18).

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1. Metal Oxide Desulfurization (17, 19).

$$RNHCSNHR + HgO\,(PbO) \longrightarrow RN{=}C{=}NR + HgS\,(PbS) + H_2O$$

2. Sodium Hypochlorite Oxidation (20).

$$RNHCSNHR + 4NaOCl + 2NaOH \longrightarrow RN{=}C{=}NR + 4NaCl + Na_2SO_4 + 2H_2O$$

3. Halogenation of thioureas and ureas followed by dehydrohalogenation of the N,N′-disubstituted carbamic chloride (21).

$$RNHCSNHR + COCl_2 \longrightarrow \left[RNHCCl(=NHR)\right]^+ Cl^- \xrightarrow[NaOH]{H_2O} RN{=}C{=}NR + NaCl$$

4. Desulfurization by treatment of thioureas with ethyl chloroformate in the presence of a tertiary amine (22).

$$RNHCSNHR + ClCOOC_2H_5 + R'_3N \longrightarrow R'_3NH^+Cl^- + \left[RNHCSCOOC_2H_5(=NR)\right]$$
$$\xrightarrow{heat} RN{=}C{=}NR + COS + C_2H_5OH$$

Carbodiimides may also be prepared by dehydration of disubstituted ureas using *p*-toluenesulfonyl chloride and pyridine (23).

$$RNHCONHR + p\text{-}CH_3C_6H_4SO_2Cl + 2C_5H_5N \longrightarrow RN{=}C{=}NR +$$
$$C_5H_5NH^+Cl^- + p\text{-}CH_3C_6H_4SO_3^- \overset{+}{H}NC_5H_5$$

Stability

In the aliphatic series, stability of the carbodiimides increases with branching of the alkyl substituents in the following order: $RCH_2 < R_2CH < R_3C$. Liquid methyl *n*-propylcarbodiimide becomes turbid after standing a month and is almost completely solidified after 12 months, while methyl-tert.-butylcarbodiimide may be distilled after standing 3 years. Unsaturation in the substituting group decreases the stability of the carbodiimide (24).

The aromatic carbodiimides also vary in stability. Di-*p*-iodophenylcarbodiimide polymerizes very readily; pure, crystalline di-*p*-tolylcarbodiimide is stable for several months; and di-*p*-dimethylaminophenylcarbodiimide is stable over a period of several years (25), 26).

The structures of the carbodiimide decomposition or polymerization products have not been investigated extensively. A method is available, however, for the estimation of carbodiimides which utilizes the quantitative reaction between oxalic acid and carbodiimides (27).

Reactions

1. Synthesis of Amides.—The reaction of carbodiimides with equimolar amounts of amines and carboxylic acids to form amides is not sensitive to moisture (1), while

$$RN{=}C{=}NR + R'COOH + R''NH_2 \longrightarrow RNHCONHR + R'CONHR''$$

procedures such as those involving mixed anhydride formation must be carried out under anhydrous conditions. N,N′-dicyclohexylurea, formed from dicyclohexyldicarbodiimide, a reagent used extensively in peptide synthesis, has a very low solubility in most organic and aqueous solvents and is usually easily separated. In the use of this reaction in the synthesis of high-molecular-weight peptides, N,N′-dicyclohexylurea and the peptide may have similar solubility properties. Separation may be realized by utilizing 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide or 1-cyclohexyl-3-(2-morpholinoethyl) carbodiimide metho-*p*-toluenesulfonate (18), since the corresponding urea derivatives are soluble in water and are easily separated from the peptide.

Khorana has discussed the mechanism of amide formation and has pointed out some of the difficulties encountered when carbodiimides are used in peptide synthesis (28).

In the final step of their penicillin V synthesis, Sheehan and Henery-Logan treated *D*-α-phenoxymethylpenicilloic acid hydrate with dicyclohexylcarbodiimide in dioxane–water solution in the presence of potassium hydroxide to obtain the cyclization product, potassium phenoxymethylpenicillinate, in 10 to 12% yield (29).

Prior to the use of carbodiimides (30), successful synthesis of peptides containing hydroxylamino acids had been accomplished only through a multistep procedure (azide method).

2. Synthesis of Pyro- and Polyphosphates.—Diphenyl and di-*p*-tolylcarbodiimide react with mono- and diesters of phosphoric acid at room temperature to yield the corresponding di- and tetraesters of pyrophosphoric acid. The reaction is rapid and the yields are almost quantitative (3).

$$(R'O)_2POOH + RN{=}C{=}NR \longrightarrow RNHCONHR + [(R'O)_2PO]_2O$$

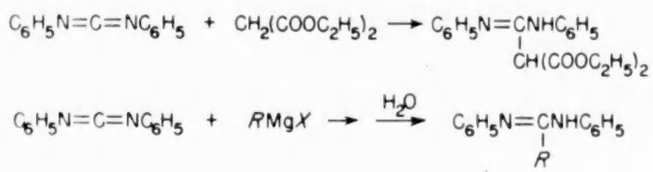
Tetra-*p*-nitrophenyl Pyrophosphate, which can be prepared by treatment of di-*p*-nitrophenyl hydrogen phosphate with di-*p*-tolylcarbodiimide, has been shown to be a powerful phosphorylating reagent for alcohols (11).

A one-step synthesis of adenosine diphosphate (ADP) and adenosine triphosphate (ATP) has been successfully carried out by treatment of a mixture of adenosine monophosphate and 85% phosphoric acid with excess dicyclohexylcarbodiimide (31).

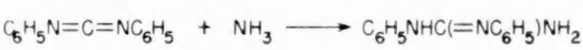
Recently, Moffatt and Khorana described the use of dicyclohexylcarbodiimide in the preparation of adenosine-2′,3′-cyclic-5′-phosphoromorpholidate, a key intermediate in the total synthesis of Coenzyme A (10).

3. Esterification of Carboxylic Acids.—Carboxylic acid esters are prepared in good yield by condensing equimolar amounts of carboxylic acid and an alcohol in the presence of a carbodiimide at a temperature below 100° C. (2, 32, 33).

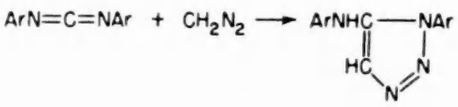
9. Synthesis of Substituted amidines.—Malonic ester and related compounds in the presence of catalytic amounts of their sodio derivative react with diphenylcarbodiimide to form the corresponding substituted amidines (7) Grignard reagents undergo 1,2-addition to form alkylamidines (39).



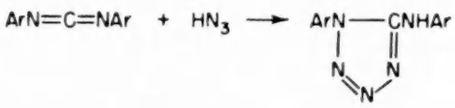
10. Synthesis of Guanidines.—Ammonia reacts with diphenylcarbodiimide to form diphenylguanidine (35).



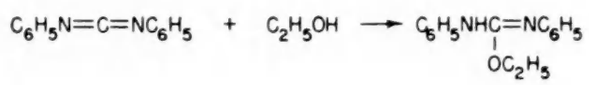
11. Synthesis of Triazoles and Tetrazoles.—Aromatic carbodiimides react with diazomethane to give triazole derivatives (40).



Reactions of aromatic carbodiimides with hydrazoic acid lead to tetrazole formation (41).



12. Pseudourea Formation from Alcohols.—Alcohols react with diphenylcarbodiimide at elevated temperatures to form O-alkylpseudoureas (42).



References

1. Sheehan, J. C., and Hess, G. P., *J. Am. Chem. Soc.*, **77**, 1067-1068 (1955).
2. Schmidt, E., and Schnegg, R. (To Farbenfabriken Bayer A.-G.) U. S. 2,686,180 (1954); *Chem. Abstr.*, **48**, 12169 (1954).
3. Khorana, H. G., and Todd, A. R., *J. Chem. Soc.* (*London*), pp. 2257-2260 (1953).
4. Khorana, H. G., *Can. J. Chem.*, **31**, 585-588 (1953).
5. Zetzsche, F., and Fredrich, A., *Ber.*, **73B**, 1114 1123 (1940).
6. Cotter, R. J., Sauers, C. K., and Whelan J. M., *J. Org. Chem.*, **26**, 10-15 (1961).
7. Tishchenko, V. E., and Koshkin, N. V., *J. Gen. Chem.* (*U.S.S.R.*), **4**, 1021-1026 (1934); *Chem. Abstr.*, **29**, 2153 (1935).
8. Zetzsche, F., and Baum, G., *Ber.*, **75B**, 100-105 (1942).

References (continued)

9. Gish, D. T., Katsoyannis, P. G., Hess, G. P., and Stedman, R. J., *J. Am. Chem. Soc.*, **78**, 5954 (1956).
10. Moffatt, J. G., and Khorana, H. G., *Ibid.*, **83**, 663-675 (1961).
11. Moffatt, J. G., and Khorana, H. G., *Ibid.*, **79**, 3741-3746 (1957).
12. Khorana, H. G., *J. Chem. Soc.* (*London*), pp. 2081-2088 (1952).
13. Khorana, H. G., *Chem. Revs.*, **53**, 145-166 (1953).
14. Franssen, A., *Bull. soc. chim. France*, **43**, 177-193 (1928).
15. Wotiz, J. H., *J. Am. Chem. Soc.*, **73**, 693-696 (1951).
16. Stevens, C. L., and French, J. C., *Ibid.*, **75**, 657-660 (1953).
17. Hünig, S., Lehmann, H., and Grimmer, G., *Ann.*, **579**, 77-86 (1953).
18. Sheehan, J. C., and Hlavka, J. J., *J. Org. Chem.*, **21**, 439-441 (1956).
19. Schmidt, E., and Moosmüller, F., *Ann.*, **597**, 235-240 (1955).
20. Schmidt, E., Seefelder, M., Jennen, R. G., Striewsky, W., and Martius, H.von, *Ibid.*, **571**, 83-86 (1951).
21. Eilingsfeld, H., Seefelder, M., and Weidinger, H., *Angew. Chem.*, **72**, 836-845 (1960).
22. Coles, R. F., and Levine, H. A. (To General Aniline and Film Corp.), U. S. 2,942,025 (1960); *Chem. Abstr.*, **54**, 24464 (1960).
23. Amiard, G., and Heymès, R., *Bull. soc. chim. France*, pp. 1360-1361 (1956). (Series 6.)
24. Schmidt, E., Striewsky, W., Hitzler, F., and Jennen, R. G., *Ann.*, **560**, 222-231 (1948).
25. Zetzsche, F., Lüscher, E., and Meyer, H. E., *Ber.*, **71B**, 1088-1093 (1938).
26. Zetzsche, F., Meyer, H. E., Overbeck, H., and Nerger, W., *Ibid.*, **71B**, 1512-1516 (1938).
27. Zetzsche, F., and Fredrich, A., *Ibid.*, **72B**, 363-365 (1939).
28. Khorana, H. G., *Chemistry and Industry*, pp. 1087-1088 (1955).
29. Sheehan, J. C., and Henery-Logan, K. R., *J. Am. Chem. Soc.*, **79**, 1262-1263 (1957).
30. Sheehan, J. C., Goodman, M., and Hess, G. P., *Ibid.*, **78**, 1367-1369 (1956).
31. Khorana, H. G., *Ibid.*, **76**, 3517-3522 (1954).
32. Schmidt, E., and Schnegg, R. (To Farbenfabriken Bayer A.-G.), Ger. 825,684 (1951); *Chem. Abstr.*, **49**, 3258 (1955).
33. Farbenfabriken Bayer A.-G., Brit. 691,808 (1953); *Ibid.*, **48**, 7637 (1954).
34. Lacey, R. N., and Ward, W. R., *J. Chem. Soc.* (*London*), pp. 2134-2141 (1958).
35. Weith, W., *Ber.* **7**, 10-16 (1874).
36. Zetzsche, F., and Pinske, H., *Ibid.*, **74B**, 1022-1024 (1941).
37. Busch, M., Blume, G., and Pungs, E., *J. prakt. Chem.*, (*2*) **79**, 513-546 (1909).
38. Laubenheimer, A., *Ber.*, **13**, 2155-2159 (1880).
39. Busch, M., and Hobein, R., *Ibid.*, **40**, 4296-4298 (1907).
40. Rotter, R., and Schaudy, E., *Monatsh.*, **58**, 245-248 (1931).
41. Stolle, R., *Ber.* **55B**, 1289-1297 (1922).
42. Lengfeld, F., and Stieglitz, J., *Ibid.*, **27**, 926-927 (1894).